| Notice of Allowability | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/828,352 | JOHNSON, MICHAEL R. | |
| | Examiner | Art Unit | |
| | Zachary C. Tucker | 1624 | |

***-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--***

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☐ This communication is responsive to _____.

2. ☒ The allowed claim(s) is/are *125-202*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS ( as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review ( PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   **Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 21Apr04,19Jul06
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

***Preliminary Amendments***

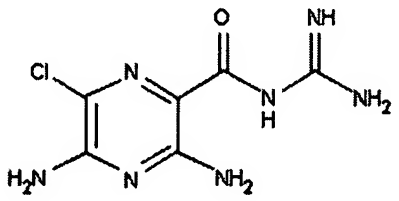
Preliminary Amendments filed 21 April 2004 and 4 November 2004, requesting changes to the claims and specification, have been entered.

***Allowable Subject Matter***

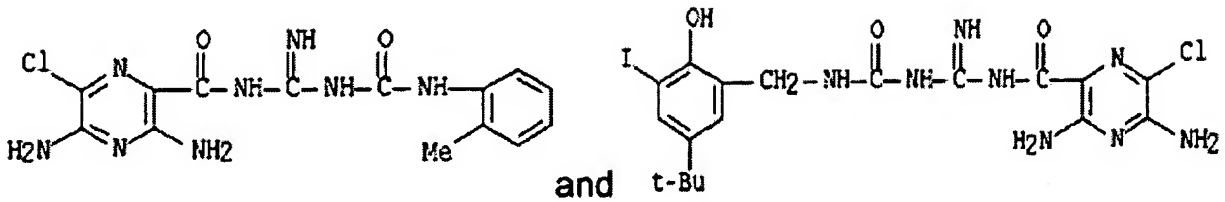
Claims 125-202 are allowed.

The following is an examiner's statement of reasons for allowance:

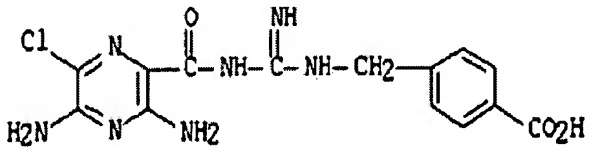
Compounds according to the instant claims are not known from the prior art, nor is there any teaching in the prior art which would render it obvious to make such compounds. Thus, the compositions and method according to the present invention are novel and similarly unobvious. Formula (I) compounds according to the instant claims are based on a core structural motif which is derived from the sodium channel blocking diuretic drug commonly known as "amiloride," which is known from US 3,313,813 (Cragoe, Jr.). Amiloride has the structure shown:



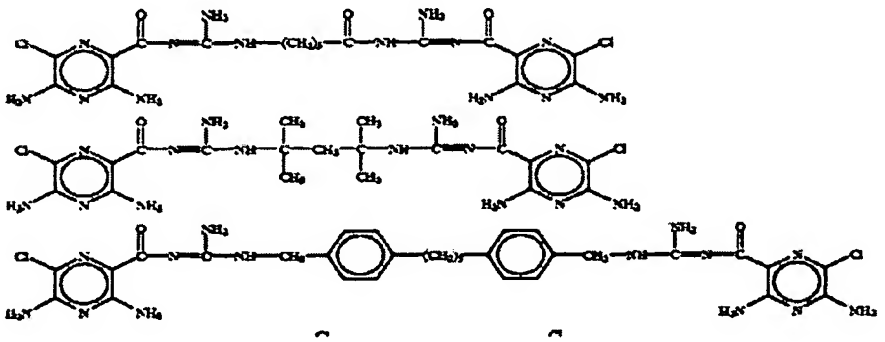

Derivatives of amiloride have been reported in the literature wherein the guanidyl $-NH_2$ group is functionalized with alkylphenyl groups, wherein the phenyl is further substituted with halogen, methyl or amino groups. Such compounds, for example, are known from US 4,085,211 (Cragoe, Jr. et al), which describes compounds of the following structures (appearing on the next page):

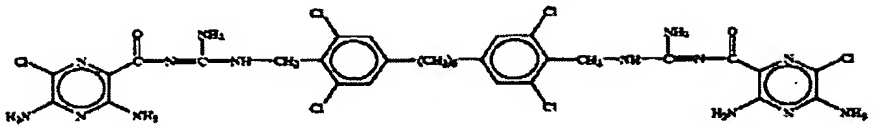


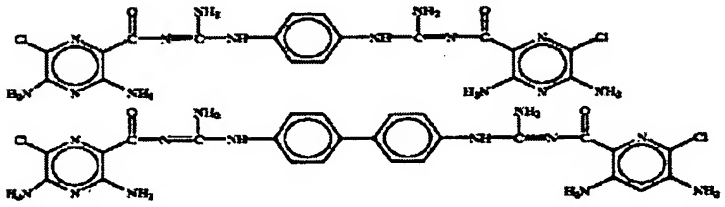
One such alkylphenyl-guanidine functionalized derivative of amiloride, wherein the phenyl group is substituted with carboxylic acid group was reported in Kleyman et al, "Distinct epitopes on amiloride. II. Variably restricted epitopes defined by monoclonal anti-amiloride antibodies" American Journal of Physiology, vol. 260(2, Pt. 1), pages C271-C276 (1991). The compound has this structure:



US 6,475,509 (Boucher, Jr. et al) is pertinent for its disclosure of *bis*-amiloride compounds having the following structural formulae, none of which is within the scope of any of the presently allowed claims:







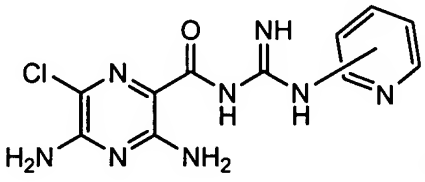
Another particularly pertinent disclosure is Velly et al, "Effects of amiloride and its analogues on [3H]batrachotoxinin-A 20-α benzoate binding, [3H]tetracaine binding and 22 Na influx" European Journal of Pharmacology, vol. 149, no- 1-2, 1988, pages 97-105. Velly et al reports several derivatives of amiloride which are not disclosed in any of the other references, cited hereinabove. Structures of these compounds are shown in Table I on page 99 of the reference. Velley et al teach a number of alkylphenyl-guanidine derivatives along the lines of the above-cited Kleyman et al article.

The compounds according to the allowed claims are different from all of those described in the preceding, most notably because the derivitizations of the guanidyl $-NH_2$ group is with a pyridine ring-containing element. At least one of the variables "Q" in the formula (A) specified in instant claim 125 must be a nitrogen atom, providing for a pyridine ring. This pyridine ring must be further substituted with one variable $R^5$, which is chosen from a group of many alternatives.

Amiloride derivatives, similar to those described in the preceding, except the phenyl ring is a pyridine ring (like the compounds according to the present invention) are known from the prior art.

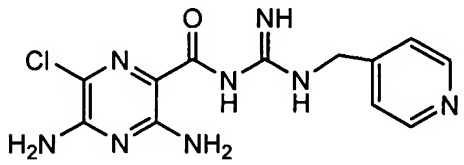
US 4,264,406 (Cragoe, Jr. et al) teaches a series of heterocyclically substituted amiloride derivatives, wherein the guanidyl $-NH_2$ is bonded to a heterocyclic ring of varying

identities. In the examples is described two compounds following structural formula shown:

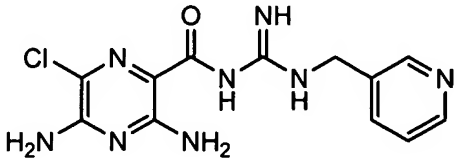


(where pyridyl is bonded *via* 2- and 3-positions)

Cocks et al, "Amiloride analogues cause endothelium-dependent relaxation in the canine coronary artery *in vitro*; possible role of $Na^+/Ca^{2+}$ exchange" British Journal of Pharmacology, vol. 95(1), pages 67-76 (1988) reports a compound represented by the diagram below:



A structural isomer of the compound depicted in the immediately preceding paragraph, wherein the pyridine ring is bonded *via* the 3-position instead of the 4-position, whose structure is shown below, is disclose in many patents and scientific journal articles, by many inventors and researchers:



This compound is disclosed in US 3,573,306 (Shepard et al), US 3,539,569 (Tull and Pollack), US 3,472,848 (Cragoe, Jr. et al), and in many others.

Though pyridylmethyl substituted amiloride derivatives like those described herein are known, none of the references disclosing such compounds actually describes any compound embraced by the instant claims, and none provides any suggestion to place any of the permitted $R^5$ groups on the pyridine ring. It is noted also that formula (I) according

to instant claim 125 provides for identities in "X," "Y," "$R^2$," "$R^1$" and the linker moiety in (A) which provides for much more than only derivatives of amiloride, wherein the pyrazine ring is 3,5-diamino-6-chloro-substituted.

Applicant has been granted one other U.S. patent related to the instant application, wherein the "Q" containing ring is a pyridine ring – US 6,995,160. Upon review of the claims in that patent, it is apparent that there is no overlap between the compounds of the patent and those according to the instant claims, because the definitions for the variable $R^5$ are different. Therefore, a double patenting rejection is not seen as proper.

Insofar as applicant's other issued U.S. patents disclosing and claiming sodium channel blocker compounds based on the same core amiloride motif, none of those patents poses any double patenting issues with respect to the instant claims, although the language of the method claims in these issued patents is the same, the compounds with which the methods are practiced are different. There is no overlap between any of the instantly claimed subject matter and subject matter claimed in applicant's other patents in the present series.

These issued patents are:

US 6,858,614, US 6,828,615, US 6,903,105, US 6,995,160, US 7,026,325, US 7,030,117 and US 7,064,129.

The therapeutic utility of the compounds according to the instant claims is mediated by sodium channel blockade due to the compounds' sodium channel blocking effect. Blockade of sodium channels causes an increase in mucous clearance and increased hydration. A representative number of diseases and conditions treated by the pharmacological effect of blocking sodium channels is set out at page 22.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

***Conclusion***

All Post-Allowance Correspondence concerning this application must be mailed to:

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Or you can fax them to the Office of Patent Publications at 703-872-9306, in order to expedite the handling of such correspondence as amendments under 37 CFR 1.312; information disclosure statements, and formal drawings. Sending Post-Allowance papers to Technology Center 1600 will only cause delays in matching papers with the case.

For information concerning status of correspondence sent after receipt of the Notice of Allowance, please contact the Correspondence Branch at (703) 305-8027. The Notice of Allowance also has an insert containing contact information on other items, including Issue Fees, receipt of formal drawings and the status of the application.

Zachary C. Tucker
Primary Examiner
Art Unit 1624

zt